AMENDMENTS TO THE DRAWINGS:

Replacement Figures 5A-D, 9C, 10 11 and 12 are appended to this paper. The replacement drawing figures have better images.

Attachment: Replacement Sheets

REMARKS

The Examiner is thanked for the due consideration given the application. Clearer drawing figures have been provided.

Claims 28, 30-34, 37, 38 and 40-63 are pending in the application. Rejoinder is noted with appreciation. The claims of record have been amended to better set forth the invention being claimed. New claim 62 sets forth the allowable subject matter of claims 42, 43 and 45 in independent form. New independent claim 63 generally corresponds to the subject matter of the allowed Australian application and includes setting forth the species of the agents

No new matter is believed to be added to the application by this amendment.

Rejection Under 356 USC §112, Second Paragraph (Maintained)

Claim 40 has been rejected under 35 USC §112, second paragraph as being indefinite. This rejection is respectfully traversed.

The Office Action asserts that the term "potential toxins" is indefinite. Although this point is not conceded for reasons of record, this term has been removed from claim 40 in order to expedite prosecution on the merits.

As a result, the claims are clear, definite and have full antecedent basis.

This rejection is believed to be overcome, and withdrawal thereof is respectfully requested.

Art Rejections

Claims 28, 30-32, 34, 38-41, 44, 46-53 and 61 remain rejected under 35 USC §102(b) as being anticipated by PRECHEL et al. (*Cancer Letters*, 1995, 92: 235-242) as evidenced by CAR et al. (*Toxicologic Pathology*, 1999, Vol. 24: 58-63).

Claim 33 remain rejected under 35 USC §103(a) as being unpatentable over PRECHEL et al. in view of DE ASUA et al. (*Proc. Natl. Acad. Sci. USA*, 1973, 70: 1388-1392) and KAMEI (*Cell Biol. Int. Rep.*, Jan 1987, 11(1): 35-41).

Claim 37 remains rejected under 35 USC §103(a) as being unpatentable over PRECHEL et al. in view of TAMI et al. (U.S. Patent 4,744,985).

Claims 47-54, 56, 57, 59 and 60 are newly rejected under 35 USC §102(b) as being anticipated by WO 01/00585 (TJOTTA et al.) as evidenced by SZUCS et al. (*Bulletin WHO* 1988 66: 729-737).

Claims 47-53, 56, 57, 59 and 60 are newly rejected under 35 USC §102(b) as being anticipated by GERNER et al. (U.S. Patent 6,258,845).

Claims 47-53, 56, 57, 59 and 60 are newly rejected under 35 USC §102(b) as being anticipated by HAYASHI et al. (U.S. Patent 4,880,742) as evidenced by McCLAIN et al. (*FASEB Journal*, 1995 9: 1345-1354).

Claims 47, 48, 59 and 60 are newly rejected under 35 USC §102(b) as being anticipated by DE ASUA et al. (of record).

Claims 47, 48, 59 and 60 are newly rejected under 35 USC §102(b) as being anticipated by KAMEI (of record).

Claim 58 is newly rejected under 35 USC §103(a) as being unpatentable over TJOTTA in view of TANNOCK (*Experimental Chemotherapy*).

These rejections are respectfully traversed.

Distinctions of the present invention over the previously applied art have been made of record in the application which, for brevity, are not repeated here.

At page 13, third full paragraph the Office Action asserts:

> *Applicant's arguments have been considered, but have not been found persuasive because the claims are a method for testing and selecting an agent to determine whether said agent inhibits or stimulates clonal growth. The claimed method is trying to identify these inhibitors or stimulators. Thus, the claims are not limited to using an agent that has activity on clonal growth for testing or agents recited in the specification. Thus, given that Prechel et al. and Tamei teach the clonal tests as previously set forth, it would have been obvious to use the Ehrlich tumor cells of Tamei in the method of Prechel et al. for the reasons previously set forth. Thus, Applicant's [arguments] are not found persuasive and the rejection is maintained.*

However, independent claims 28 and 61 have been amended to add subject matter that the Office infers may be allowable.

This includes specifying the agent as *"an agent that has an activity on clonal growth,"* seeding *"solitary"* cells on *"soft"* agar and a *"low gelling temperature gel"*. Support for these amendments can be found at pages 27 and 40 of the specification.

The claimed invention is thus clearly allowable over the previously applied art.

In regards to the new rejection over TJOTTA et al. as evidenced by SZUCS et al. set forth on page 31, the Office Action states:

> *[I]t is noted that the clonal mitotic inhibitor of claims 47, 50 and 59 are products identified by a process and the patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claim. In re Thorpe, 227 USPQ 964 (Fed. Cir. 1985). Thus, the clonal mitotic inhibitor used in claims 47, 50 and 59 need not be selected by the method of claim 28.*
>
> *WO 01/00585 (Tjotta et al. 4 January 2001) teach inhibition of T-lymphocyte growth, T¬cell tumor growth and Kaposi's sarcoma with pyrazolidinols, including 4-OH-OPB. WO 01/00585 teaches treating subjects with HIV and Herpes infection with 4-OH-OPB, Which would be before HIV infected cells are piling up given the undefined time before HIV infected cells are piling up. See Abstract, pages 1-10, and claims 1-12. WO 01/00585 teaches administering additional antiviral agents with 4-OH-OPB to inhibit drug resistance. See claim 5 and ¶ bridging p. Sand 6.*

WO01/00585 teaches adding fresh growth media to MT-4 cells, Additionally, Szucs et al. teach that MT-4 are grown in serum. See p. 730-1st col. Thus, one of skill in the art would immediately recognize that MT-4 cells are grown in serum. See Example 12. Although, WO01/00585 does not specifically teach that T-lymphocyte growth and Kaposi's sarcoma is clonal cell growth, in the absence of a limiting definition of clonal cell growth, WO 01/00585 anticipates the claims.

Although the reference does not specifically state that 4-OH-OPB was administered as an initial treatment in order to inhibit metastasis of a cancer, the claimed method appears to be the same as the prior art product, absent a showing of unobvious differences as the administered 4¬OH-OPB would inherently have this property . The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977).

This argument by the Office is based on two paragraphs [0028] and [0031] in TJOTTA et al.:

[0028] *However, in a particularly preferred embodiment of the invention, a pyrazolidinol according to the*

invention is administered at a dose sufficient to suppress T-lymphocyte (CD4 and CD8 cell) growth (e.g. a daily dose of 0.1 to 10 μmol/kg) for a period of 1 to 14 days, preferably 2 to 7 days at intervals of at least 3 months, preferably at least 9 months, e.g. 10 to 18 months. In this way the patient's immune system may be "refreshed" by removal of the preponderance of T-lymphocytes directed to HIV antigens. Such a treatment indeed is novel and forms a further aspect of the invention. Viewed from this aspect the invention provides a method of combating HIV infection which comprises administering to an HIV-infected patient a T-lymphocyte growth suppressing agent, e.g. a pyrazolidinol, in an amount sufficient to suppress T-lymphocyte growth in said patient for a period sufficient to reduce the T-lymphocyte concentration in the lymphatic system, e.g. the lymph nodes, in said patient by at least 25%, more preferably at least 50%, said administration being repeated at intervals of at least 3 months, preferably at least 9 months.

[0031]*Besides HIV, the pyrazolidinols of the invention may be used to combat other viral infections, especially retroviral infections but also infections by togaviridea, reoviridea, picornaviridea, hantaviridea, orthomyxoviridea, paramyxoviridea, mononegaviralis, viral hepatitis, haemorrhagic fevers, flaviviridea, viral encephalitis, coronaviridea, calciviridea, adenoviridea, papovaviridea, arboviridea, pox virus, rhabdoviridea, herpes virus and arenaviridea. The pyrazolidinols of the invention may in particular be used to combat viral infections*

of CD4 cells, e.g. HIV-1, HIV-2, HTLV-I, HTLV-II and herpes viruses, for example to combat AIDS, T-cell tumours (e.g. Sezary Syndrome, mycosis fungoides and T-cell lymphoma, and particularly CD4 cell tumours), tropic spastic paraparesis, and Karposi's sarcoma. Moreover despite not being of the accepted formula for NSAIDs (which would require an acid proton in place of R1X1 at the 4-position), they may be used as anti-inflammatory drugs. All these uses form aspects of the invention.

It is evident from patent TJOTTA (paragraph 31, 7 lines from end) that: "*The pyrazolidinols of the invention may in particular be used to combat viral infections of CD4 cells, e.g. HIV-1, HIV-2, HTLV-I, HTLV-II and herpes viruses, for example to combat AIDS, T-cell tumours (e.g. Sezary Syndrome, mycosis fungoides and T-cell lymphoma, and particularly CD4 cell tumours), tropic spastic paraparesis, and Karposi's sarcoma.*"

This paragraph teaches that the pyrazolidinols should combat: T-cell tumours (e.g. Sezary Syndrome, mycosis fungoides and T-cell lymphoma, and particularly CD4 cell tumours).

This is 5 tumors. This shows that at the time TJOTTA was filed nobody knew that growth of tumors are not affected by 4-OH-OPB. Therefore, it is evident that the knowledge where tumors neutralized the effect of what we now call specific clonal inhibitors was not a part of prior art at that time. Even the growth of T4-cell tumors will not be affected by specific clonal

inhibitors since the claimed patent applies the T4 cell line MT4 that reacted just as other cells in culture. The inhibitory growth effect of the best known specimen of these compounds, 4-O-OPB, was much more pronounced on sparsely seeded cells than on cultures containing many cells (see experiment no. 14).

The present invention is thus clearly distinguished from the prior art such that there is neither anticipation nor *prima facie* unpatentability.

These rejections are believed to be overcome and withdrawal thereof is respectfully requested.

The Drawings (New Objection)

The drawings have been objected to as not being legible (Figures 5A-D, 9C, 10, 11 and 12). Appropriate substitute drawing figures have been submitted.

Claim Objections (New)

Claims 32, 39, 48, 51 and 60 have been objected to as containing informalities. The comments in the Office Action have been considered, and the claims have been appropriately amended. Also, claim 39 has been canceled.

Rejections Under 35 USC §112 (New)

Claims 52, 54 and 55 have been rejected under 35 USC §112, second paragraph, as being indefinite (item 8).

Claims 48, 49, 51-53 and 55 have been rejected under 35 USC §112, first paragraph as not being enabled (item 9).

Claim 60 has been rejected under 35 USC §112, first paragraph as not being enabled (item 9, page 17).

Claims 48, 49, 51-53 and 60 have been rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement (item 10).

Claims 54-56 have been rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement (item 11).

These rejections are respectfully traversed.

Regarding the indefiniteness rejection in item 8, claim 52 haws been amended to better correspond to claim 51 in accordance with the Examiner's kind suggestion.

The term "piling up" in claim 54 has been replaced with the term "proliferate", which is clear.

Claim 55 has been amended to improve the antecedent basis.

The claims are thus clear, definite and have full antecedent basis within the *aegis* of 35 USC §112, second paragraph.

Regarding enablement (item 9) the Office Action comments at page 20, third paragraph:

> *One of skill in the art cannot extrapolate the teachings of the specification to enable the full scope of the claims to use all of the compounds claimed in claims 48, 51 and 60 clonal mitotic inhibitors and stimulators in any cell type under any*

condition because some of the claimed compounds have been only tested for their activity in vitro against one cultured cell type (S100T1). These effects cannot be predictably extrapolated to clonal inhibition or stimulation to any cell type under any condition because cultured cells can produce artifactual responses that are not reflective of the in vivo response of cells and cells are heterogeneous in the phenotypes and responses to drugs like clonal mitotic inhibitors or stimulators.

In response, the applicant notes that it is correct that the screening part of the claimed test is not enough for accepting the compounds as adequate treatment for stopping metastases. Therefore, a test in living organisms is essential and is included in the patent claim (see Experiments 7-9). At the moment none of the tested compounds have shown as good results as 4-OH-OPB *in vitro* and *in vivo*.

However, less activity in this respect may also be interesting and it can explain why persons using for instance acetylsalicylic acid (see experiment 15 and 16) is known to be partly protected against development of cancer. On the other hand, detected activities as stimulators of clonal growth (see Experiment 26) may be important when testing food or other compounds in our environment, since this activity is expected to have the opposite effect; increasing the incidence of cancer or stimulating the progression of this disease.

The *in vitro* test on cell lines is not as bad as given voice to in the Official Action, since the best clonal inhibitor, 4-OH-OPB, shows no breakthrough in the agar cultures of clones with ability to grow even when under treatment. The best example of the opposite is Colchicine that is not stopping all clones, but let a few grow even at high concentrations of Colchicine. In our experiments this compound is rather not able to save mice transplanted with Ehrlich's cancer cells (see Experiment 18).

In addition the Office Action states in the first paragraph of page 23 that: "*Taken together, these observations suggest that the biological properties of cell lines can differ markedly from the cancer cells from which they were derived.*"

Cancer cells with or without changes is not the question. All cells that the inventor has tested, even normal cells in culture or in the organism (see Experiment 10) react the same way on specific clonal inhibition. Single or very few immune-cells in the spleen among other non-identical immune-cells are inhibited. Collocated identical cells in other organs in the animal (liver, muscles, skin, peritoneum etc) are not inhibited by specific clonal inhibitor and can not abrogate the effect of a specific clonal inhibitor on scattered identical cells in close contact (see Experiments 7-9). This stresses the importance of the main invention, a basic biological and medical principle with many practical consequences.

On the second paragraph of page 25 the Office action asserts:

> *Additionally as drawn to claim 55 wherein 4-OH-OPB is administered to a subject with chronic infections or AIDS after removing the collocated infected cells, one of skill in the art would not predictably expect to remove the collocated infected cells because HIV and the herpes simplex viruses form latent infections in cells that are not removed from the subject by treatments for these diseases used at the time the invention was made. In particular, Dybul et al. (MMWR Recommendations and Reports May 17, 2002, p.1-71) teach that eradication of HIV infection cannot be achieved with available anti-retroviral regimens, because the pool of latently infected CD4+ T cells is established early during infection and persists with a long half-life. See p. 13. Additionally, Efstathiou and Preston (Virus Res. 2005, 111:108-119) teach that a key characteristic of all herpes viruses is their ability to establish life-long latency within the infected host. See p. 108. Additionally, Smith et al. (Antiviral Res. 200152:19-24) teach that herpes simplex virus drugs like acyclovir have no effect on the latent HSV infection once established. See ¶ bridging p. 20 and 21 and p. 23. Thus, given the resistance of latent HIV and HSV infections to anti-viral treatments known at the time the invention was made, one of skill in the art would not be able to remove the collocated infected cells with methods known in the art or taught in the specification without undue experimentation.*

In response, applicant respectfully notes that it is correct that it is not considered possible to remove all infected cells from HIV infected patients. However, it might be possible to remove a large portion of them, e.g., by using antibodies with toxic groups to cells expressing HIV antigens or by simply using cytotoxins. The latter method is used in connection with bone marrow transplantation, but might be risky.

At the moment there is no final proof, but many indications that removing many of these cells with inactive HIV would dilute their local crowding and allow better inhibitory effect of 4-OH-OPB on the production of active HIV. This viewpoint is a central part of the invention and is not known in previous art, e.g., in TJOTTA.

For Herpes a method similar to the first one for HIV might also be possible, and may be easier since the crowding of chronically infected cells in nerve ganglia probably is less than the crowding of cells containing HIV genome in the lymphatic organs.

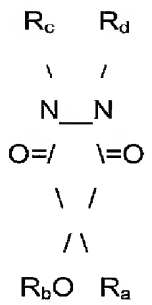
At the third paragraph of page 26 the Office Action asserts:

> *Claims 48, 49, 51-53 are broadly drawn to a method for inhibiting clonal cell growth or clonal cell growth in a subject, comprising: administering to the cells or subject an effective amount of a clonal mitotic inhibitor, wherein the clonal mitotic inhibitors are selected from the group consisting of*

4-OH-OPB, colchicine, Ibuprofen, Naproxen, Acetyl salicylic acid, p¬hydroxy-azobenzene, 2-Butyl-2-hydroxy-N-(4- hydroxy-phenyl)-N'-phenyl malonamide, 1,2¬diphenyl-4-hydroxy-4- [2-(phenylsulfinyl)ethyl]-3,5-pyrazolidinedione, and analogues thereof.

However, analogues of 4-OH-OPB are described in the patent application on pages 45-47 of PCT/NO2003/000335:

Some 4-hydroxy-3,5-dioxo-pyrazolidines are described in the literature for treatment of HIV infections and some other viral infections, tropic spastic paraparesis, autoimmune diseases, transplantation rejection and special tumours as Sezary syndrome, mycosis fungoides, T-cell lymphoma, and Kaposis sarcoma. The example used in the described experiments is 4-OH-OPB, which is 4-butyl-4-hydroxy-2 (p-hydroxyphenyl)-1-phenyl-3,5-pyrazolidinedione with the general formula:



where Ra - Rd might be defined as in Table 1.

The immunosuppressive and antineoplastic drugs available might have inhibiting effects on clonability of tumour cells, and possibly also inhibit metastatic migration.

However, collocated cells might partly or fully neutralise the effect on clonability if the substances

have low toxicity. This knowledge is probably very important when treating patients, especially those with malignant diseases. Since most of the cytotoxic drugs used against cancer also are expected to have a smaller or greater effect against clonal growth, there are possibilities of finding suitable candidates among them that could be used in reduced, less toxic concentrations over long time periods giving effects as described for clonal inhibitors.

Therefore, the substances exemplified in the following might be potential candidates and is currently tested by the method of the invention in the inventor's laboratory.

R_a	R_b	R_c	R_d
H	H	H	C_6H_5
H	H	C_6H_5	C_6H_5
CH_3	H	H	C_6H_5
CH_3	H	H	$-CH_2-C6H_5$
CH_3	H	H	$P-CH_30-C6H_4$
CH_3	H	H	$p-C1-C6H_4$
C_2H_5	H	H	C_6H_5
C_2H_5	H	C_6H_5	C_6H_5
C_2H_5	H	H	N-methyl-piperidin-4-yl
iC_3H7	H	H	C_6H_5
nC_3H7	H	H	C_6H_5
nC_3H7	H	C_6H_5	C_6H_5
C_3H7	H	H	5-phenyl-triazol-1-yl
C_4H9	H	H	C_6H_5
C_4H9	H	C_6H_5	C_6H_5
C_4H9	H	o $OH-C_6H_4$	o $OH-C6H_4$
C_4H9	OH	m $OH-C_6H_4$	m $OH-C_6H_4$
C_4H9	OH	p $OH-C_6H_4$	p $OH-C_6H_4$
C_4H9	H	H	N-methyl-piperidin-4-yl
C_5H_{11}	H	H	C_6H_5
C_5H_{11}	H	C_6H_5	C_6H_5
C_5H_{11}	H	H	5-phenyl-triazol-1-yl
Cyclohexyl	H	H	C_6H_5
Phenyl	H	H	C_6H_5
Phenyl	H	C_6H_5	C_6H_5
Benzyl	H	H	C_6H_5
Benzyl	H	C_6H_5	C_6H_5
$CH_3CO(CH_2)_2$	H	C_6H_5	C_6H_5
$(CH_3)_2C=CH-$	H	C_6H_5	C_6H_5
$(CH_2)_2C=CHCH2-$	H	C_6H_5	C_6H_5
$C6H_5SOCH_2CH_2-$	H	C_6H_5	C_6H_5
Pyrrolidin-1-yl	H	C_6H_5	C_6H_5
Piperidin-1-yl	H	C_6H_5	C_6H_5
Morpholip-4-yl	H	C_6H_5	C_6H_5

It is thus believed that the instant claims of the present invention comply with the written description requirement and are sufficiently enabled such that one of skill in the art can practice the claimed invention without recourse to undue experimentation.

These rejections are believed to be overcome, and withdrawal thereof is respectfully requested.

Conclusion

The objections and rejections are believed to have been overcome, obviated or rendered moot and no issues remain. The Examiner is accordingly respectfully requested to place the application in condition for allowance and to issue a Notice of Allowability.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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REG/jr

APPENDIX:

The Appendix includes the following items:

☒ - Replacement Sheets for Figures 5A-D, 9C, 10 11 and 12